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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,548	08/25/2003	Javier Saez-Valero	104664-50037	5163

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/648,548	SAEZ-VALERO ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response to the restriction requirement and amendment filed 7-21-04 have been entered into the record. Claims 1-18 have been cancelled and new claims 19-29 have been added.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. The first line of the specification is missing the reference to parent 09/829,446.

Drawings

The drawings in this application have been approved by the Draftsperson.

Information Disclosure Statement

The information disclosure statement filed 8-25-03 has been considered. An initialed copy is enclosed.

Election/Restrictions

The restriction requirement is moot in view of the cancellation of the non-elected subject matter and amendment to the claims accompanying the response of 7-21-04.

Claim Objections

Claims 20-25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The steps recited in the dependent claim 19 does not measure relative affinity as recited in claim 19. The "level" measurement is not a measure of affinity and as such, these claims fail to further limit the independent claim. Additionally, they do not futher limit step (2) of claim 19 because it does not measure the relative affinity of both the concanavalin A and Lens Culinaris binding butyrylcholinesterase.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite "wherein a level of unbound Bche of greater than 5% is indicative of the presence of elevated levels of the Bche with an altered glycosylation pattern.", or as further limiting, greater than 6.4%, greater than 7.5% and greater than 8%. The specification specifically provides for a specific range on as recited in Table 1 on page 8 of the specification. This range does not support "greater than 5%, 6.4% or 7.5%" because it clearly has an upper limit. The specification provides in the original claims for "at least about eight percent". Again the term provides for "about" which implicitly provides for an upper limit. As such, the claims as not originally filed are not supported by the specification as originally filed. This issue is best resolved by Applicants pointing to the specification by page an line number where specific written description support for the now claimed subject material can be found.

Claims 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not define the term affinity or relative affinity. The term as commonly used in the chemical, medical and biological arts is understood to

alternatively mean: 1 - an attractive for between substances or particles that causes them to enter into and remain in chemical combination (Merriam-Webster Online), 2 - in biological and biochemical fields this term is generally a measure of the attraction of one biomolecule toward another molecule either to alter it, destroy it or form a compound with it (Life Science Dictionary), 3 - a measure of the binding strength between two molecules (Drug Discovery), or 4- the strength of noncovalent chemical binding between two substances measured by the dissociation constant of the complex (On-line Medical Dictionary). The specification does not teach any conventional measurement of the affinity of butyrylcholinesterase (BuChe) in any of (1) the concanavalin A (ConA) - binding form, (2) the ConA non-binding form, (3) the Lens Culinaris (LCA) - binding form or (4) the LCA non-binding form for either the normal BuChe or altered glycosylation pattern BuChe. As such, one skilled in the art would recognize that Applicants were not in possession of the claimed invention given the common meaning of the term "affinity" as used in the biological and biochemical fields. Binding versus not binding is not a measure of affinity as defined by the art, which is represented an association or dissociation constant, or other binding force measurement.

Claims 19-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the diagnosis of Alzheimer's disease in a patient comprising the steps of providing a sample of biological fluid from a patient, detecting the presence of total butyrylcholineserase in the sample, detecting the presence of butyrylcholinesterase unbound to both concanavalin A (conA) and *Lens culinaris* (LCA) lectins, determining the percent butyrylcholinesterase unbound to both conA and LCA wherein a increase in the percent of butyrylcholinesterase unbound to conA and a decrease in the percent of butyrylcholinesterase unbound to LCA as compared to normal is indicative of

Alzheimer disease and further wherein the total and unbound butyrylcholinesterase is determined by enzymatic activity or monoclonal antibody binding, it does not reasonably provide enablement for patterns of altered glycosylation of butyrylcholinesterase in general or relative binding affinities to any lectin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The teachings of the specification are limited to a single "pattern" of altered lectin binding by butyrylcholinesterase. The specification teaches by measuring the percent of butyrylcholinesterase "unbound" as a proportion of the total amount in the sample fluid as compared to a normal control, a pattern of altered lectin binding emerges for only two lectins (see specification Table 1 page 8). The specification teaches only two instances of differences from normal occur in all of the lectin binding. The first is the percent unbound for conA and percent unbound to LCA. The total amounts of each were not compared. The percent bound was not compared. As such, the only pattern taught by the specification is that for percent unbound for conA and LCA. The specification fails to teach the actual chemical structure of the glycosylation on each of the butyrylcholinesterase "unbound" to the lectin. The specification fails to teach the actual chemical structure of the glycosylation on each of the types of butyrylcholinesterase that is bound to the lectin. The specification does not enable other chemical means of determining glycosylation structure (HPLC analysis, spectrophotometry, enzymatic). The specification does not each the "affinity" of the altered BuChe or for the unaltered BuChe as commonly defined in the art. In order to perform these other methods, one would have to *a priori* have knowledge of the specific chemical structure of the particular glycosylation on both normal and altered butyrylcholinesterase and have measured the affinity constants for the specifically

claimed lectins. This specification provides no written description of these chemical structures and therefore does not enable these other means of determining altered structure. The specification does not teach the affinity constants and therefore does not enable this means of discrimination of the altered versus unaltered forms of glycosylated BuChe. Further, since the lectin binding analysis on Table 1 of the specification clearly demonstrates that the normal person has both the lectin-binding and non-lectin binding forms of butyrylcholinesterase, the determination of the mere presence or absence of any "altered" glycosylation form does not provide for diagnosis of Alzheimer's disease. As to the isoforms of butyrylcholinesterase with altered glycosylation, the specification is devoid of any correlation of different isoforms with Alzheimer's disease. It is noted that it is the correlation step that provides for diagnosis by correlation with an unknown undefined unaltered glycosylation pattern in the claims. One skilled in the art would have to provided inventive input to discover if any isoforms were in fact "altered" in glycosylation and then determine a means to measure such and finally determine if there is in fact a correlation of any isoform with Alzheimer's disease with normal controls. The teachings for acetylcholinesterase do not directly correlate with butyrylcholinesterase. This is evidenced by the conflicting data for lectin binding on Tables 1 and 2. This data demonstrates that butyrylcholinesterase and acetylcholinesterase do not have the same lectin-binding patterns and therefore the teachings of patterns, isoforms and amounts are not directly applicable from one enzyme to another. Therefore, the skilled artisan could not rely on the teachings of acetylcholinesterase to enable the isoform diagnosis using butyrylcholinesterase. Therefore in view of the lack of written description for "affinity" measurements in the specification as filed and in the absence of further guidance from Applicants, one skilled in the art could not perform the method as claimed without undue experimentation.

Claims 19-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 19 and every claim dependent thereon (20-29), the term "relative affinity" is prima facie indefinite because the claims do not set forth the fixed point to which the increase or decrease in affinity is compared to. That is, the claim does not establish the affinity values of the BuChe with the unaltered glycosylation pattern. The claims do not establish the base point for comparison (i.e. the affinity of the unaltered glycosylation BuChe pattern). As such, the metes and bounds of the "relative affinity" cannot be established because the point for comparison is not set forth in the claims.

As to claim 20-25, the claims do not properly further limit the specific steps of claim 19. The terms of claim 19 are set in "relative affinity" and none of the steps set forth in claim 20 provides for an ultimate "affinity" measurement. Claim 20 measures levels whereas claim 19 measures affinity. These two measurements are not the same. Affinity is not a measure of percent bound. It is a force measurement of the interaction of the glycosylated BuChe with the affinity lectin. In other words, claim 19 requires a relative comparison of the affinity of ConA binding of the altered glycosylation BuChe with the affinity of ConA binding of the unaltered glycosylation BuChe. None of the steps of claim 20 provide for this measurement. Further, the measurement steps of does not provide for a relative measurement as recited in claim 19, the independent claim recites both ConA and LCA however, claim 20 recites only ConA and does not correlate how it is relative to the unaltered glycosylation BuChe pattern of step (2) that it is supposed to further limit. As currently written, this dependent claim is not interpretable in context of claim 19 from which it depends. As to claims 20-29, these dependent

claims are confusing because they begin with the recitation of the indefinite article "A" meaning any method, but then attempt to further limit the method to particular steps or proceedures. Amendment of these dependent claims to change "A" to "The" would obviate this issue.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-F 6:30 am - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645